Radon and Lung Cancer Risk: Taking Stock at the Millenium

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Radon is a well-established human carcinogen for which extensive data are available, extending into the range of exposures experienced by the general population. Mounting epidemiologic evidence on radon and lung cancer risk, now available from more than 20 different studies of underground miners and complementary laboratory findings, indicates that risks are linear in exposure without threshold. Radon is also a ubiquitous indoor air pollutant in homes, and risk projections imply that radon is the second leading cause of lung cancer after smoking. Recommended control strategies in the United States and other countries, which include testing of most homes and mitigation of those exceeding guideline levels, have been controversial. Further research is needed, drawing on molecular and cellular approaches and continuing the follow-up of the underground miner cohorts, and scientists should work toward constructing mechanistically based models that combine epidemiologic and experimental data to yield risk estimates with enhanced certainty. *Key words*: lung cancer, radon, radon progeny, risk assessment. — *Environ Health Perspect* 108(suppl 4):635–641 (2000). *http://ehpnet1.niehs.nih.gov/docs/2000/suppl-4/635-641samet/abstract.html*

Radon, discovered early in the 20th century as an emanation from radium, is now a well-characterized human carcinogen. An extensive scientific literature based in experimental and observational data addresses mechanisms of action at the cellular and molecular levels, exposures and doses in occupational and general environmental settings, and cancer risk, along with modifiers of risk such as smoking. This literature has been frequently reviewed and summarized, most recently in the report of the National Research Council's Biological Effects of Ionizing Radiation (BEIR) VI Committee (*1*) released in 1998. The final report was published in 1999. That report comprehensively reviewed the literature and offered new models for estimating the lung cancer risk associated with radon exposure. The present review does not replicate that coverage, and readers seeking a summary of the scientific evidence should turn to the BEIR VI report or other recent reviews (*2,3*).

After a brief synthesis of the current state of knowledge of radon and cancer, this review looks to future needs for research on radon, both for public policy purposes and for advancing understanding of radon carcinogenesis. In fact, our knowledge of the risk posed by radon is relatively advanced compared to that on many other human carcinogens. However, the public policy implications of indoor radon are so sweeping that a high level of certainty has been sought by policymakers about the risks of the low levels of exposures generally found in homes. Questions have been raised about the scientific basis for the U.S. Environmental Protection Agency's (U.S. EPA) Radon Program since its inception in the early 1980s (*4*). Mounting epidemiologic and laboratory research have steadily reduced critical uncertainties, and further gains in knowledge can be projected. Mechanistic research on the consequences of cellular irradiation by alpha particles, directly responsible for the causation of cancer by radon, will enhance certainty and eventually support the development of biologically based models. In the wealth of data already available and with these exciting prospects for evolution of the evidence, radon carcinogenesis offers a superb model for linking from research to risk assessment to policy.

Radon and Lung Cancer: An Overview

The story of radon as a cause of lung cancer is a long one with historical accounts documenting a fatal lung disease centuries ago in miners working in the Erz Mountains of Eastern Europe (*5*). Over a century ago, the miners were found to have thoracic malignancy, later identified as primary lung cancer. By early in the 20th century, levels of radon in the mines in this region were measured and found to be quite high; the hypothesis was soon advanced that radon was the cause of the unusually high rates of lung cancer. Although not uniformly accepted initially, as the findings of epidemiologic studies of underground miners were reported from the 1950s on, there soon was substantial evidence showing that radon was a cause of occupational lung cancer (*1,5*). In fact, the more recent concern about radon in the air of homes was initially driven by the strong evidence that radon causes lung cancer in underground miners.

Radon is a noble and inert gas resulting from the decay of naturally occurring uranium-238. With a half-life of over 3 days, radon has time to diffuse through rock and soil after it forms and before undergoing further decay into its particulate progeny. In mines, it enters the air from the ore or is brought into the mine dissolved in water. In homes, the principal source is soil gas, which penetrates through cracks or sumps in basements or around a concrete slab. Because uranium-238 is universally present in the earth, radon is a ubiquitous indoor air pollutant, and it is also present in outdoor air, albeit at far lower concentrations. Infrequently, building materials or water also may contribute significantly to indoor concentrations.

Radon is an alpha emitter that decays with a half-life of about 3.5 days to a short-lived series of progeny (Figure 1) (*1*). Unlike radon, the progeny are solid and form into small molecular clusters or attach to aerosols in the air after their formation. The inhaled particulate progeny may be deposited in the lung on the respiratory epithelium; radon by contrast is largely exhaled, although some radon is absorbed through the lung. Radon itself is not responsible for the critical dose of radioactivity delivered to the lung that causes cancer. While radon was initially thought to be the direct cause of the lung cancer in the miners, Bale (*6*) and Harley (*7*) recognized in the early 1950s that alpha particle emissions from radon progeny and not from radon itself were responsible for the critical dose of radiation delivered to the lung. Alpha decays of two radioisotopes in the decay chain, polonium-218 and polonium-214 (Figure 1), deliver the energy to target cells in the respiratory epithelium that is considered to cause radon-associated lung cancer (*8*). Alpha particles, equivalent to a helium nucleus, are charged and have a high mass. Although their range of penetration into tissues is limited, they are highly effective at damaging the genetic material of cells. As reviewed in the report of the BEIR VI Committee (*1*), passage of even a single alpha particle through a cell can cause permanent genetic change in the cell.

Evidence on radon and lung cancer risk is now available from approximately 20 different epidemiologic studies of underground miners,

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including 11 studies that provide quantitative information on the exposure–response relationship between exposure to radon progeny and lung cancer risk (*1,9*). Occupational risks of radon-caused lung cancer have been described in many reports on the findings of the individual studies and in several pooled analyses of the data from the 11 studies with quantitative information (*1,10*). There is a surprising degree of consistency among the risks estimated in these studies; the risk coefficients span approximately a single order of magnitude, in spite of substantial methodologic differences among the studies (*1*). In general, the temporal patterns of excess risk following exposure are also similar among the studies; that is, risks change in a similar fashion with time since exposure and with age of the individual.

Although radon progeny are now a well-recognized occupational carcinogen, radon became a topic of controversy again in the 1970s and 1980s because it was found to be a ubiquitous indoor air pollutant in homes, and recommended control strategies in the United States and other countries included testing of most homes and mitigation of those levels exceeding suggested guidelines (*4*). Radon was found to be present in indoor air as early as the 1950s, but potential health implications received little notice until several decades later. The problem first received the greatest attention in Scandinavia, but homes with radon levels of concern have now been identified in other countries of Europe and in North America. Housing surveys show that radon is ubiquitous and that concentrations tend to follow a log-normal distribution (Figure 2). Policies are now in place in many countries to manage the lung cancer risk associated with indoor radon. These policies involve identification and mitigation of radon levels in homes with concentrations above guideline values and use of construction techniques that reduce radon concentrations. Since these policies potentially extend to almost all residential housing, their scientific base has been challenged, as has their cost effectiveness.

Initially, risks of indoor radon were estimated primarily by extrapolating the risks observed in the studies of underground miners to the exposures sustained by the general population indoors. In this risk assessment approach, key uncertainties reflected the use of risk estimates from relatively short-term exposures at concentrations substantially above those typically found in homes, the extension of estimates from men, largely smokers, to the entire population, and differing dosimetry of radon progeny for the circumstances of exposures in mines and in homes. Linear nonthreshold models were used for the extrapolation from higher to lower exposures, which invited the criticism that risks were overestimated. Lung models were used to address the potential uncertainty from differing dosimetries in homes and mines, with the finding that exposure–dose relations were quite comparable for the miners and for the general population (*8*).

To develop risk estimates directly from the general population, case–control studies were initiated beginning in the 1980s (*1,5*). The basic design of these studies involved comparison of estimated radon exposures for lung cancer cases with those of appropriate controls. Radon exposures were estimated by making measurements of radon concentrations, generally over several months to a year, in the current and former residences of cases and controls. The case–control studies were soon recognized as being subject to substantial bias toward a null finding because of unavoidable errors in the exposure estimates; such errors arose from missing data and errors in the radon measurements (*11*). Consequently, plans were made for pooling the data from the individual studies (*12*). Initial pooling of data from North America and Europe is now in progress and a pooling of all of the studies should be completed by approximately 2002. In the meantime, the findings of the completed studies have been combined using meta-analysis (*1,13*). The risk estimate derived from the eight completed studies is indicative of an effect fully consistent with the risk extrapolations from the miner studies (Figure 3).

Although risk management for indoor radon remains controversial, the evidence on radon and lung cancer is now very extensive. Initially, epidemiologic and other research was driven by the need to characterize the

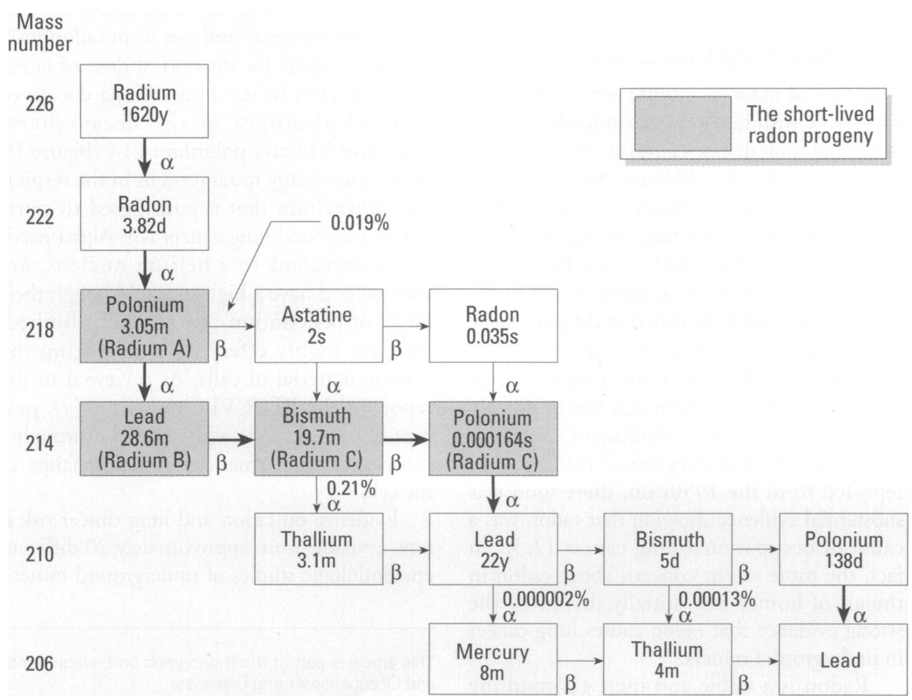

Figure 1. The radon-decay chain. An arrow pointing downward indicates decay by alpha-particle emission; an arrow pointing to the right indicates decay by beta-particle emission. The historical symbols for the nuclides are in parentheses below the modern symbols. Most decay takes place along the unbranched chain marked with thick arrows. The negligible percentage of decay along the thin arrows is shown at critical points. The end of the chain, lead-206, is stable not radioactive. Half-lives of each isotope are shown as seconds (s), minutes (m), days (d), or years (y). Modified from the National Research Council (*1*).

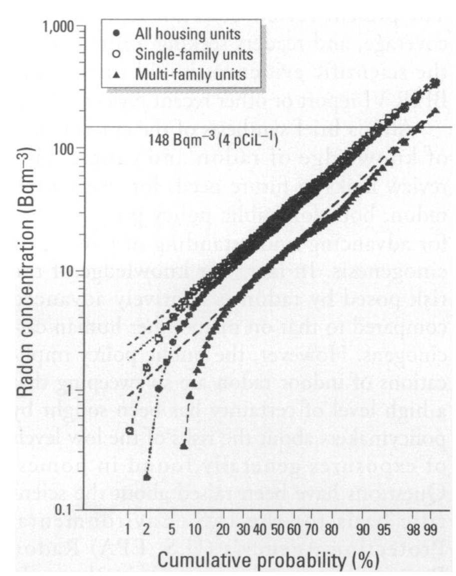

Figure 2. Distribution of radon concentrations in U.S. homes. Modified from the U.S. EPA (*4*).

risks faced by underground miners in order to set exposure limits that would have acceptable risks. This work emphasized epidemiologic approaches, but animal studies were also conducted to confirm the hazard and to address the modifying effects of such factors as the presence of ore dust and diesel exhaust, cigarette smoking, and dose rate (*14*). More recently, research has reflected the need to understand better the risks posed to the general population by indoor radon. Epidemiologic studies have been conducted to assess directly the general population's risk of lung cancer from indoor radon; laboratory studies using molecular and cellular approaches have been conducted to better understand the mechanism of radon carcinogenesis and to address key uncertainties in assessment of the risks of indoor radon.

Over the last several decades, risk models have been developed for risk assessment and risk management of indoor radon. However, lung cancer risk in underground miners has long been of interest; in fact, the first attempt to quantify risk was made by Evans and Goodman (*15*) in their 1940 report based on the radon measurements made in the Schneeburg and Joachimsthal mines. Key reports have come from the International Commission for Radiological Protection (ICRP), the National Council for Radiation Protection and Measurements, and the BEIR Committees of the U.S. National Research Council. Samet (*16*) has reviewed the evolution of risk assessment for radon and lung cancer. To illustrate the contemporary approach to radon risk assessment, the models developed by the BEIR VI Committee are described below.

Conceptually, the BEIR VI Committee extended the approach used a decade earlier by the BEIR IV Committee, i.e., developing an empiric, time-dependent model for lung cancer risk from the miner data and then extending that model to the general population with consideration of the possibility of differing exposure–dose relations in homes and in mines and of smoking, the most critical potential modifying factor. The BEIR VI Committee used the pooled data set from the 11 miner cohorts and the 1994 analysis of Lubin et al. (*10*) as a starting point for developing its risk models (*1*). The pooled data set included more than 2,700 lung cancer deaths among 68,000 miners followed for nearly 1.2 million person-years of observation. This data set was substantially larger than that considered by the BEIR IV Committee.

Most analyses were based on a linear excess relative risk (ERR) model:

$$RR = 1 + \beta w \text{ or } ERR = \beta w,$$

where RR is relative risk, β is a parameter measuring the unit increase in ERR per unit increase in w, and w is cumulative exposure to radon progeny in WLM (working level months is the unit of exposure used for undergound miners; lifetime exposure indoors is approximately 14 WLM). As in the BEIR IV analysis, ERR was linearly related to cumulative exposure to radon progeny. The ERR/WLM varied significantly with other factors; it decreased with attained age, time since exposure, and time after cessation of exposure but was not affected significantly by age at first exposure. Over a wide range of total cumulative exposures to radon progeny, lung cancer risk was increased as exposure rate declined, confirming the pattern reported from the Colorado Plateau study (*17*), and supporting the prior hypothesis of an inverse dose-rate effect (*18*). The inverse dose-rate effect implies that the lower rates of exposure, typical of homes, could increase risk more than projected from estimates made at the generally higher exposures experienced by the miners. The extent of the information available at lower levels of exposure permitted analyses of risks in a range of exposures of greatest relevance to exposures associated with indoor radon. With the data restricted to cumulative exposures below 200 WLM, there was no evidence for departure from a linear model and the exposures were in a range at which an inverse dose-rate effect was not expected on a biophysical basis (*1*).

The BEIR VI (*1*) report provides risk estimates for various scenarios of exposure to radon and also makes projections of the burden of lung cancer in the United States attributable to radon progeny (Table 1). These estimates are provided in Table 1, which includes the figures for the total population and for smokers and never-smokers separately. The estimates for smokers and never-smokers are based on the assumption of a submultiplicative combined effect of smoking and radon progeny. The submultiplicative relationship was estimated from the studies with data available on both smoking and exposure to radon progeny; it implies synergism between the two factors, but the degree of synergism is less than fully multiplicative. Estimates based on the BEIR IV model are included in the tables along with estimates based on fitting a constant relative risk model to the data at exposures less than 50 WLM, the lowest level of exposure with sufficient data available for analysis. The BEIR VI report also includes a quantitative uncertainty analysis.

These estimates confirm that radon progeny should be considered a significant cause of lung cancer in the United States. The attributable risks are higher on a percentage basis for never-smokers than smokers, reflecting the submultiplicative interaction between smoking and radon progeny. The numbers of

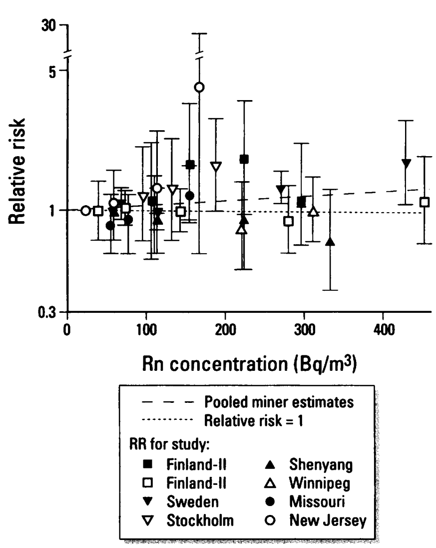

Figure 3. Relative risks from 8 lung cancer case–control studies of indoor radon. - - - -, extrapolation of risk from miners (*10*). ·····, relative risk of 1.

Table 1. Estimated attributable risk[a] for lung cancer death from domestic exposure to radon using 1985–1989 U.S. population mortality rates based on selected risk models.

Model	Population	Ever-smokers[b]	Never-smokers[b]
Males			
Committee's preferred models			
Exposure–age–concentration	0.141	0.125	0.258
Exposure–age–duration	0.099	0.087	0.189
Other models			
CRR[c] (< 50 WLM)	0.109	0.096	0.209
BEIR IV	0.082	0.071	0.158
Females			
Committee's preferred models			
Exposure–age–concentration	0.153	0.137	0.269
Exposure–age–duration	0.108	0.096	0.197
Other models			
CRR (< 50 WLM)	0.114	0.101	0.209
BEIR IV	0.087	0.077	0.163

CRR, constant relative risk.
[a]The risk of lung cancer death attributed to radon in populations exposed to radon divided by the total risk of lung cancer death in a population. [b]Based on a submultiplicative relationship between tobacco and radon. Data from the National Research Council (*1*).

attributable cancer deaths are far higher in smokers than in never-smokers. Of the lung cancer deaths attributed to radon exposure, only a minority can be prevented by current risk management strategies, as the total number of deaths attributed can, in theory, be prevented only by lowering levels of radon progeny indoors to outdoor values. For the United States, about one-third of the radon-related lung cancer deaths are attributed to concentrations above the current guideline of the U.S. EPA.

Open Questions Concerning Radon and Lung Cancer

As evident from even this brief review, we have a broad and rich evidence base on radon and lung cancer, one that has proved sufficient for developing policies for radon control. Yet, policy makers are seeking greater certainty and there are still open scientific questions to be investigated. Additionally, there is the potential for combining laboratory-based understanding of mechanisms with observational data to develop a true, biologically based risk model. These questions and potential research approaches are discussed in the next section.

What Is the Mechanism of Radon Carcinogenesis?

We are poised to make substantial advances in our understanding of mechanisms of carcinogenesis by alpha particles, which are directly responsible for the induction of lung cancer by radon. The BEIR VI Report (*1*) provides an overview of recent advances in the molecular and cellular basis of cancer causation by alpha particles and directly links these advances to their risk assessment implications. This synthesis makes clear the linkages between molecular and cellular research and key uncertainties in risk assessment: the assumption of a linear nonthreshold model at the lowest levels of exposure and the magnitude and existence of dose-rate effects at low levels of exposure. Experimental systems have also been designed to explore combined effects of radon exposure and tobacco smoking, but these models cannot replicate the complex and sustained exposure to carcinogens and irritants typical of human smoking.

New experimental methods involving single-cell irradiation with alpha particles appear particularly promising as tools for exploring the effects of alpha particles on the cell (*19*). Using this experimental model, it is possible to characterize effects on cells using single particles of varying energy and to explore the consequences of multiple versus single hits to the cell nucleus. Permanent cellular changes following single-cell irradiation were considered by the BEIR VI Committee as evidence of the appropriateness of assuming a linear nonthreshold relationship between exposure and lung cancer risk. Further advances in our understanding of the basis of radon carcinogenesis are likely to bring the greatest gain in certainty for risk models for the future, as we have already completed a relatively complete synthesis of the epidemiologic evidence.

What Is the Risk of Typical Indoor Radon Concentrations?

In the United States and other countries for which survey data are available, the concentrations of radon in homes follow an approximately log normal distribution (Figure 2). For risk management purposes, we consequently need estimates of the risks of the high end of the distribution (which overlaps substantially with the concentrations at which miners were exposed) and of the risks at typical indoor levels (which are much lower than those to which the miners were exposed in the epidemiologic studies). The population's burden of attributable risk is driven by the broad end of the distribution, which is centered around the geometric mean, whereas clearly unacceptable individual risks come from the upper end of the distribution.

This risk estimation problem has been approached by *a*) extending the exposure–response relationship for radon progeny exposure and lung cancer observed in the miners to the general population; and *b*) attempting to directly estimate risk to the general population by conducting case–control studies. The former approach is subject to the principal uncertainties arising from the generalization of risks observed in male miners, differing dosimetry of radon progeny in homes and mines, and extrapolation from higher to lower exposures. The latter approach, using risk estimates from case–control studies, has proved more difficult than anticipated when the studies were initiated. Daunting problems in estimating exposures to radon indoors markedly blunt the sensitivity of the case–control studies and limit the precision of risk estimates from their data (*9,11,20*). These problems include finding and gaining access to residences and assuming that contemporaneously measured concentrations reflect past values. The uncertainties in both approaches to estimating the risks of lower levels of indoor radon continue as a source of controversy and of weakness in the scientific foundation for managing the risk of indoor radon.

The epidemiologic evidence from the miners will become stronger as more follow-up time is accrued, particularly from the more recent cohorts with the lowest exposure. Additional cohort studies, particularly in Czechoslovakia (*21*) and the former East Germany (*22*), may also be informative. As the limitations of the individual case–control studies were recognized (*11*), plans were made to pool the results of the studies for risk estimation. Although the findings of the individual studies reported to date seemingly have been inconsistent, when construed (improperly) as positive or negative, meta-analysis shows the findings to be reasonably consistent and with evidence of a positive dose–response relationship, similar to those predicted from the miner data (*1,13*). Plans have now been completed to pool the data from the case–control studies at the individual participant level. This pooling will bring this line of investigation to a close, giving the greatest power and precision presently achievable.

The observational evidence may be strengthened by improved methods for exposure estimation and by using emerging methods for estimating exposure. The exposure estimates in the epidemiologic studies of miners are based on limited and incomplete data and pragmatic approaches [reviewed by the National Research Council (*1*)]. Undoubtedly there is substantial random error in the exposure estimates and possibly systematic error as well (e.g., systematic over- or underestimation of some exposures). This problem has long been recognized and biodosimetric methods have been developed as one potential solution, including measurement of lead-210 (the long-lived radioisotope that ends the radon progeny decay series) in red blood cells and in bone, by use of autopsy materials, or by skull counting. The sensitivity of skull counting has been enhanced (*23*), although not yet to levels sufficient for the lower end of miner exposure. Nonetheless, skull counting offers a potential approach for assessing the degree of error affecting exposure estimates in the epidemiologic studies and making adjustments using statistical methods considered below. Using the skull-counting method is currently being explored in studies of Chinese tin miners and New Mexico uranium miners.

The problems of exposure estimation in the case–control studies may be partially surmounted using glass (e.g., covering pictures) as an exposure indicator. Long-lived progeny embedded in the surface of glass over time emit alpha particles, which can be counted as an index of the concentration of radon to which the glass has been exposed (*24,25*). This approach has now been incorporated into several of the case–control studies (*26,27*). In a case–control study in Missouri, Alavanja et al. (*27*) found a significant, positive relationship between radon exposure and lung cancer risk, using glass-based exposure estimates, but not with estimates based on radon concentration in air. This finding suggests that exposure misclassification was reduced by using the glass-based estimates. This technique might be retrospectively used in other case–control studies to estimate the degree of exposure misclassification to accomplish adjustment.

With new statistical methods for considering measurement error, adjustments can be made to risk estimates (*28*). In the BEIR VI report, Thomas and colleagues (*29*) describe one approach that is undergoing further elaboration and Spiegleman and Logan (*30*) also apply measurement error correction methods to uranium miner data. These methods will inflate risk estimates in comparison with those derived from the uncorrected estimates used in the analyses to date.

Advances in the understanding of the molecular and cellular basis of carcinogenesis by alpha particles offer the greatest promise for reducing uncertainty in radon risk estimates. Together, microdosimetric considerations and experimental findings support the theory that a single alpha particle can permanently change cellular DNA (*1*). The assumption of a nonthreshold and linear model at low doses already appears quite tenable (*1*). The application of methods for single-cell irradiation will continue to inform risk assessment. For example, Miller et al. (*31*) examined the frequency of cell transformation following exposure of cell nuclei to exactly one alpha particle, compared with an average of one particle under a Poisson distribution. The rate of transformation was substantially lower with exactly one hit, leading the investigators to suggest that risk estimates made at higher exposures could overestimate risks at low exposures, where only one hit can be expected. This research is illustrative of the type of experiment that directly addresses a key uncertainty in risk estimates for radon (*19,32*).

We should be moving toward development of biologically based risk models, based on an underlying theory of radon carcinogenesis. Findings from the alpha particle irradiation studies will prove useful in developing such models. Moolgavkar et al. (*33*) and Luebeck et al. (*34*) have already applied the two-stage model of carcinogenesis to data from underground miners, illustrating the potential for biologically based modeling of epidemiologic data. Parallel analyses of animal data also have been carried out (*35*). Advances in the underlying biologic basis for such models will strengthen this approach.

Is Radon a Global Public Health Problem?

Throughout the world, particularly in countries in temperate and colder climates, indoor radon is probably a dominant contributor to radiation exposure (*36*). A review of some recent literature shows that there are numerous surveys documenting indoor concentrations of radon in developing and developed countries around the world (Table 2). Although there is likely to be a range of potential modifying factors among these countries, particularly cigarette smoking, the risk models developed by the BEIR VI Committee and other groups remain relevant for guiding policy. Extension of these models to other countries would identify some as having an unacceptable burden of lung cancer and the world's total burden of cancers attributable to radon undoubtedly would be large if estimated. Policy development and implementation is another matter and the relevance of policies adopted in North America or Europe is uncertain. Guidance should be developed by those organizations concerned with radiation protection internationally—the ICRP and the United Nations.

How Can We Protect and Compensate Uranium Miners?

The number of men and women who mined uranium underground in the countries of the West and of the former Soviet Union will

Table 2. Indoor concentrations of radon: results of surveys.

Country	Year of survey	Dwellings surveyed (no.)	Geometric mean in pCi/L (Bq m^{-3})	Geometric SD	Max range (Bq m^{-3})
Italy (*47*)	1989–1994 - survey began in March	4,866	57 Bq m^{-3}	2.0	
Russia (*48*)	1995–1996		Bq m^{-3}: I / II / III		
	April–July		190 / 195 / 115		
	October–December		380 / 653 / 206		
	January–March		253 / 640 / 190		
Russia (*49*)	1993–1994 - in the summer; morning	105	32 Bq m^{-3}		180 Bq m^{-3}
Japan	1985 - In January two detectors	100	56.8 Bq m^{-3}	2.7	
Hiroshima and Nagasaki (*50*)	were placed in 189 houses; one detector in 11 houses. Detectors were left until October 1985	99	28.5 Bq m^{-3}	2.2	
Israel (*51*)	1995 - December	Jerusalem public school (six grades, 600 students)			> 10,000 Bq m^3
Jordan (*52*)	1995 - September–December	9 major cities (35 zones each)	Radon and thoron concentration levels Bag dosimeters - 32–107 Bq m^{-3} Cup dosimeters - 27–88 Bq m^{-3}		
Hong Kong (*53*)	1995 - late November–March 1996 1996 - August–early December	10 underground shopping centers surveyed; 58 dwelling sites	29.2 ± 7.8 Bq m^3		
Southwest England (*54*)	1989–1992	1.5 million (28,900 tumors were counted)	< 40 Bq m^3 > 230 Bq m^3		
Poland (*55*)	1991 - three months	310 detectors randomly 1,099 (lung cancer)	2.2 pCi/L	> 4 pCi/L	
Kenya (*56*)		200 water samples	^{222}Rn activity concentration ranges from 0.8 ± 0.5 to 31.7 ± 33.5 Bq L^{-1}		
Thailand (*57*)	1995 - October	387 samples			179.74 and 263.38 Bq m^{-3}
Idaho (*58*)	1994	1,300 groundwater samples	17.7 Bq L^{-1}		

SD, standard deviation.

never be known, but an estimate of about 1 million may be reasonable (*37*). In the United States, thousands worked in the Colorado Plateau region (*38*) and the peak number of underground workers in the Grants Uranium belt was as high as 4,000–5,000. We know now that several hundred thousand miners worked in the former East Germany (*39*) and the number who worked in Czechoslovakia may have been as large. In China, the epidemiologic cohort of Yunan tin miners numbers around 17,000 and this is a selected group from the total population. Relative risks and attributable risks for lung cancer in the miner cohorts are high (*1*), providing strong evidence of an epidemic of occupational lung cancer in the miners. Most certainly, there will also be high rates of silicosis and silicotuberculosis among miners, and there is still a question about whether uranium miners also develop pulmonary fibrosis (*1,40*).

Uranium exploration and mining began after World War II in the climate of urgency spawned by the Cold War and the nuclear arms competition. The historical record clearly shows that the health and safety of underground uranium miners was neglected in the United States (*38,41,42*) and almost certainly in other countries as well. Unfortunately, many former miners who developed lung cancer have not received any compensation in spite of the circumstances under which they worked. In the United States, miners or their families sought compensation through the workmens' compensation system with varying success. The Radiation Exposure Compensation Act, passed in 1990 (*41*), offers an apology to the miners and provides financial compensation to miners or their families who meet criteria for exposure and diagnosis. While the act is well-intentioned, there are evident problems in its provisions that need to be addressed through scientifically based revisions (*43*). The miner data have been analyzed to develop a risk model for this purpose, illustrating one potential approach to evidence-based compensation (*44*). The relationship between compensation schemes in other countries and the epidemiologic evidence should also be evaluated.

Uranium mining continues throughout the world, although much of the ore production is from surface mines, which fortunately results in relatively low exposures. Underground mining persists, however (*36,37*). The mounting epidemiologic and experimental evidence indicates that there is no safe level of radon exposure and a lifetime of working at current exposure limits is projected to carry an unacceptable risk (*1*). Epidemiologic surveillance of currently exposed underground miners is warranted, perhaps employing new approaches for monitoring with biomarkers (*45,46*). Current and former miners, as a population at high risk for lung cancer, are also potentially useful sources of information for studies of chemoprevention and molecular markers of the early stages of carcinogenesis.

Summary and Conclusions

The story of radon and lung cancer is remarkable for its length and its many twistings and turnings. We have long known that underground miners are at risk for lung cancer and have had evidence establishing radon as a cause of lung cancer since mid-century. A wealth of epidemiologic data from the underground miners provides a quantitative picture of the lung cancer risk caused by radon and these observational data are well buttressed in a substantial body of experimental evidence. This body of experimental and observational evidence has proved informative for estimating the risks of indoor radon, a more recent problem, and observational studies that directly estimate the risks of indoor radon indicate that the indirect approach using the miner data appears on target. In fact, the totality of the evidence on radon and lung cancer is noteworthy for its scope. There are few carcinogens for which such extensive epidemiologic data are available, particularly data extending into the range of exposures experienced by the general population.

Policies for control of radon remain under attack, however, as does their scientific basis. Further research drawing on molecular and cellular approaches and further follow-up of underground miner cohorts should help alleviate much remaining criticism. Within a few decades, we should be able to construct mechanistically based risk models that combine epidemiologic and experimental data to yield radon exposure estimates with enhanced certainty.

References and Notes

1. National Research Council. Health Effects of Exposure to Radon (BEIR VI). Washington, DC:National Academy Press, 1998.
2. Samet JM. Epidemiologic studies of ionizing radiation and cancer - past successes and future challenges. Environ Health Perspect 105:883–889 (1997).
3. Samet JM, Mapel DW. Diseases of uranium miners and other underground miners exposed to radon. In: Environmental and Occupational Medicine (Rom WN, ed). Philadelphia:Lippincott-Raven, 1998;1307–1315.
4. Cole LA. Elements of Risk: The Politics of Radon. Washington, DC:American Association for the Advancement of Science Press, 1993.
5. Samet JM. Radon and lung cancer. J Natl Cancer Inst 81:745–757 (1989).
6. Bale WF. Memorandum to the files, March 14, 1951: Hazards associated with radon and thoron. Health Phys 38:1062–1066 (1980).
7. Harley JH. Sampling and measurement of airborne daughter products of radon. Nucleonics 11:12–15 (1953).
8. National Research Council. Companion to BEIR IV Report. Washington, DC:National Academy Press, 1991.
9. Lubin JH, Boice JD Jr, Samet JM. Errors in exposure assessment, statistical power, and the interpretation of residential radon studies. Radiat Res 144:329–341 (1995).
10. Lubin JH, Boice JD Jr, Edling C, Hornung RW, Howe G, Kunz E, Kusiak RA, Morrison HI, Radford EP, Samet JM, et al. Radon and Lung Cancer Risk: A Joint Analysis of 11 Underground Miners Studies. Bethesda, MD:National Institutes of Health, 1994.
11. Lubin JH, Samet JM, Weinberg C. Design issues in epidemiologic studies of indoor exposure to radon and risk of lung cancer. Health Phys 59:807–817 (1990).
12. Samet JM, Stolwijk J, Rose SL. Summary: International Workshop on Residential Radon Epidemiology. Health Phys 60:223–227 (1991).
13. Lubin JH, Boice JDJ. Lung cancer risk from residential radon: meta-analysis of eight epidemiologic studies. J Natl Cancer Inst 89:49–57 (1997).
14. National Research Council. Health Risks of Radon and Other Internally Deposited Alpha-Emitters: BEIR IV. Washington, DC: National Academy Press, 1988.
15. Evans RD, Goodman C. Determination of the thoron content of air and its bearing of lung cancer hazards in industry. J Ind Hyg Toxicol 22:89–98 (1940).
16. Samet JM. Radon risk assessment: a perspective across the century. Toxicology (in press).
17. Hornung RW, Meinhardt TJ. Quantitative risk assessment of lung cancer in U.S. uranium miners. Health Phys 52:417–430 (1987).
18. Lubin JH, Boice JD Jr, Edling C, Hornung RW, Howe G, Kunz E, Kusiak RA, Morrison HI, Radford EP, Samet JM, et al. Radon-exposed underground miners and inverse dose-rate (protraction enhancement) effects. Health Phys 69:494–500 (1995).
19. Wu LJ, Randers-Pehrson G, Xu A, Waldren CA, Geard CR, Yu ZL, Hei TK. Targeted cytoplasmic irradiation with alpha particles induces mutations in mammalian cells. Proc Natl Acad Sci USA 96:4959–4964 (1999).
20. Lubin JH, Tomasek L, Edling C, Hornung, RW, Howe G, Kunz E, Kusiak RA, Morrison HI, Radford EP, Samet JM, et al. Estimating lung cancer mortality from residential radon using data for low exposures of miners. Radiat Res 147:126–134 (1997).
21. Sandler D. Personal communication (August 24,1999).
22. Wichmann H-E. Personal communication (August 26,1999).
23. Lauer GR, Gang QT, Lubin JH, Jun-Yao L, Kan CS, Xiang YS, Jian CZ, Yi H, WanDe G, Blot WJ. Skeletal lead ^{210}Pb levels in lung cancer among radon-exposed tin miners in southern China. Health Phys 64:253–259 (1993).
24. Samuelsson C. Retrospective determination of radon in houses. Nature 334:338–340 (1988).
25. Mahaffey JA, Parkhurst MA, Hui TE, Brownson RC, Alavanja MCR. Factors affecting use of CR-39 surface monitor technology to estimate past exposure to indoor radon. J Expo Anal Environ Epidemiol 7:490–497 (1996).
26. Field RW, Kross BC. Iowa survey of waterborne ^{222}Rn concentrations in private wells. Health Phys 74:249–252 (1998).
27. Alavanja MC, Lubin JH, Mahaffey JA, Brownson RC. Residential radon exposure and risk of lung cancer in Missouri. Am J Public Health 89:1042–1048 (1999).
28. Thomas D, Stram D, Dwyer J. Exposure measurement error: influence on exposure-disease relationships and methods of correction. Annu Rev Public Health 14:69–93 (1993).
29. Stram DO, Langholz B, Huberman M, Thomas DC. Correcting for exposure measurement error in a reanalysis of lung cancer mortality for the Colorado Plateau uranium miners cohort. Health Phys 77:265–275 (1999).
30. Spiegelman D, Logan R. Unpublished data.
31. Miller RC, Randers-Pehrson G, Geard CR, Hall EJ, Brenner DJ. The oncogenic transforming potential of the passage of single α particles through mammalian cell nuclei. Proc Natl Acad Sci USA 96:19–22 (1999).
32. Miller RC, Richards M, Brenner DJ, Hall EJ, Jostes R, Hui TE, Brooks AL. The biological effectiveness of radon-progeny alpha particles. V: Comparison of oncogenic transformation by accelerator-produced monoenergetic alpha particles and by polyenergetic alpha particles from radon progeny. Radiat Res 146:75–80 (1996).
33. Moolgavkar SH, Luebeck EG, Krewski D, Zielinski JM. Radon, cigarette smoke, and lung cancer: a re-analysis of the Colorado plateau uranium miners' data. Epidemiology 4:204–217 (1993).
34. Luebeck EG, Heidenreich WF, Hazelton WD, Paretzke HG, Moolgavkar SH. Biologically based analysis of the data for the Colorado uranium miners cohort: age, dose and dose-rate effects. Radiat Res 152:339–351 (1999).
35. Luebeck EG, Curtis SB, Cross FT, Moolgavkar SH. Two-stage model of radon-induced malignant lung tumors in rats: effects of cell killing. Radiat Res 145:163–173 (1996).
36. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Sources and Effects of Ionizing Radiation. New York:United Nations Press, 1993.
37. International Physicians for the Prevention of Nuclear War. Nuclear Wastelands: A Global Guide to Nuclear Weapons Pro-

duction and Its Health and Environmental Effects. Washington, DC:Physicians for Social Responsibility, 1995.
38. Ringholz RC. Uranium Frenzy. Boom and Bust on the Colorado Plateau. New York:W.W. Norton & Company, 1989.
39. Kahn P. A grisly archive of key cancer data. Science 93:448–451 (1993).
40. Archer VE, Renzetti AD, Doggett RS, Jarvis JQ, Colby TV. Chronic diffuse interstitial fibrosis of the lung in uranium miners. J Occup Med 40:460–474 (1998).
41. Radiation Exposure Compensation Act Committee. Public Law 101-426. October 5, 1990.
42. Proctor RN. Cancer Wars. How Politics Shapes What We Know and Don't Know About Cancer. New York:Basic Books, 1995.
43. Samet JM. Testimony before the Senate Committee on the Judiciary Hearing on Amending the Radiation Exposure Compensation Act of 1990. Available: *http://www.senate.gov/~judiciary/samet.htm* [cited 7 October 1999].
44. Human Radiation Interagency Working Group. Final report of the Radiation Exposure Compensation Act Committee. Washington, DC:U.S. Department of Energy, 1996.
45. Neft RE, Crowell RE, Gilliland FD, Murphy MM, Lane JL, Harms H, Coons T, Heaphy E, Belinsky SA, Lechner JF. Frequency of trisomy 20 in nonmalignant bronchial epithelium from lung cancer patients and cancer-free former uranium miners and smokers. Cancer Epidemiol Biomarkers Prev 7:1051–1054 (1998).
46. Crowell RE, Belinsky SA. Genetic changes in lung cancer: potential biomarkers for early detection and prevention. J Lab Clin Med 130:550–557 (1997).
47. Bochicchio F, Campos-Venuti G, Nuccetelli C, Piermattei S, Risica S, Tommasino L, Torri G. Results of the representative Italian national survey on radon indoors. Health Phys 71:741–748 (1996).
48. Zukova AS, Voronina TF, Pakulo AG, Vereiko SP. The radon levels of the living quarters in the city of Lermontov and the irradia tion doses. Gig Sanit 46:32–33 (1998).
49. Eremeeva TN. Radon and its decay products in the air of preschool institutions of Serpukhov. Med Tr Prom Ekol 9:13–17 (1996).
50. Yonehara H, Aoyama T, Radford EP, Kato H, Sakanoue M. Radon concentrations in residential housing in Hiroshima and Nagasaki. Health Phys 68:683–688 (1995).
51. Richter ED, Neeman E, Fischer I, Berdugo M, Westin JB, Kleinstern J, Margaliot M. Radon exposures in a Jerusalem public school. Environ Health Perspect 105:1411–1416 (1997).
52. Ahmad N, Matiullah, Khatibeh AJ. Comparative studies of indoor radon concentration levels in Jordan using CR-39 based bag and cup dosimeters. Health Phys 75:60–62 (1998).
53. Yu KN, Young EC, Stokes MJ, Lo CH. A survey of radon properties in underground shopping centers in Hong Kong. ApplRadiat Isot 48:863–866 (1997).
54. Etherington DJ, Pheby DF, Bray FI. An ecological study of cancer incidence and radon levels in South West England. Eur J Cancer 32A:1189–1197 (1996).
55. Jedrychowski W, Flak E, Wesolowski J, Liu KS. Relation between residential radon concentrations and housing characteristics. The Cracow Study. Cent Eur J Public Health 3:158–160 (1995).
56. Otwoma D, Mustapha AO. Measurement of ^{222}Rn concentration in Kenyan groundwater. Health Phys 74:91–95 (1998).
57. Ausoodkij B, Polpong P, Bovornkitti S. Indoor radon in Thailand: a study with particular reference to its sources. J Med Assoc Thailand 79:519–525 (1996).
58. Paulus LR, Gesell TF, Brey RR. An evaluation of ^{222}Rn concentrations in Idaho groundwater. Health Phys 74:237–241 (1998).